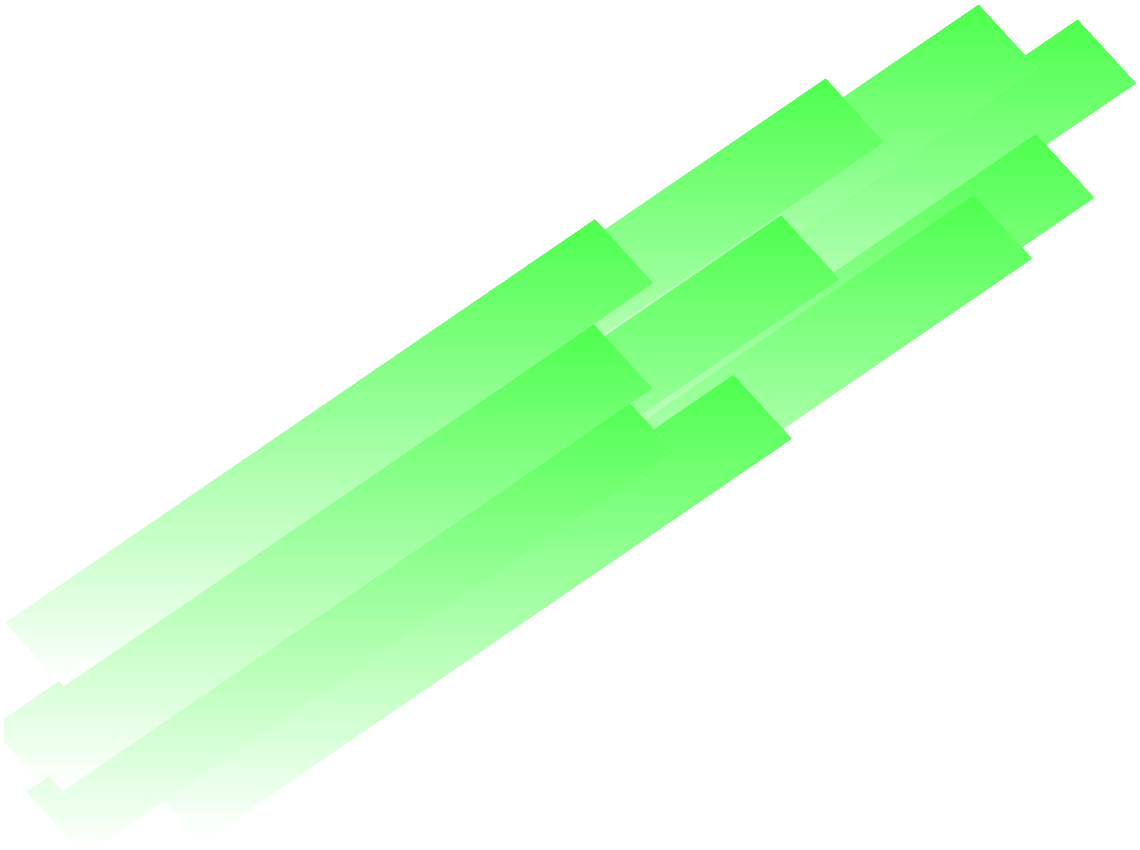
Guidance for Industry

Labeling Guidance for Cisapride Oral Suspension



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (PROPULSID®; Janssen Pharmaceutica, Inc.; 20-398/S-002; Approved December 11, 1995; Revised September 1995). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

CISAPRIDE ORAL SUSPENSION

WARNINGS

Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation have been reported in patients taking cisapride with other drugs that inhibit cytochrome P450 3A4, such as ketoconazole, itraconazole, miconazole, troleandomycin, erythromycin, fluconazole, and clarithromycin. Some of these events have been fatal. Cisapride is contraindicated in patients taking any of these drugs. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS - Drug Interactions).

DESCRIPTION

[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

Cisapride oral suspension contains cisapride as the monohydrate, which is an oral gastrointestinal prokinetic agent. Cisapride as the monohydrate is a white to slightly beige odorless powder. It is practically insoluble in water, sparingly soluble in methanol, and soluble in acetone. Each 1.04 mg of cisapride as the monohydrate is equivalent to 1 mg of cisapride. Chemically cisapride is designated as cis-4-Amino-5-chloro-*N*-[1-[3-(*p*-fluorophenoxy)propyl)-3-methoxy- *4*-piperidyl)-*o*-anisamide. Its molecular formula is $C_{23}H_{29}ClFN_3O_4 \cdot H_20$. The molecular weight is 483.97. It has the following structural formula:

[INSERT STRUCTURAL FORMULA HERE]

Each 5 mL for oral administration, contains cisapride as the monohydrate equivalent to 5 mg of cisapride. In addition, each 5 mL contains the following inactive ingredients: *[Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter ,1091> for guidance).]*

CLINICAL PHARMACOLOGY

Pharmacokinetics

Cisapride is rapidly absorbed after oral administration; peak plasma concentrations are reached 1 to 1.5 hours after dosing. The absolute bioavailability of cisapride is 35 to 40%. When gastric acidity was reduced by high dose histamine H_2 receptor blocker and sodium bicarbonate in fasting subjects, there was a decrease in the rate, and to a lesser degree the extent, of cisapride tablet absorption. (This has not been established for the suspension.) Cisapride binds to an extent of 97.5 to 98% to plasma proteins, mainly to albumin. The volume of distribution of cisapride is about 180 L, indicating extensive tissue distribution.

The plasma clearance of cisapride is about 100 mL/min. The mean terminal half-life reported for cisapride ranges from 6 to 12 hours; longer half-lives, up to 20 hours, have been reported following intravenous (IV) administration. Cisapride is metabolized mainly via the cytochrome P 450 3A4 enzyme. Cisapride is extensively metabolized; unchanged drug accounts for less than 10% of urinary and fecal recovery following oral administration. Norcisapride, formed by N-dealkylation, is the principal metabolite in plasma, feces and urine.

There was no unusual drug accumulation due to time-dependent or non-linear changes in PK. After cessation of the repeated dosing, the elimination half-lives (8 to 10 hr) were in the same order as after single dosing. There is some evidence that the degree of accumulation of cisapride and/or its metabolites may be somewhat higher in patients with hepatic or renal impairment and in elderly patients compared to young healthy volunteers, but the differences are not consistent and do not require dosage adjustment.

Pharmacodynamics

The onset of pharmacological action of cisapride is approximately 30 to 60 minutes after oral administration.

The mechanism of action of cisapride is thought to be primarily enhancement of release of acetylcholine at the myenteric plexus. Cisapride does not induce muscarinic or nicotinic receptor stimulation, nor does it inhibit acetylcholinesterase activity. It is less potent than metoclopramide in dopamine receptor-blocking effects in rats. It does not increase or decrease basal or pentagastrin-induced gastric acid secretion.

In vitro studies have shown that cisapride is a serotonin-4 (5-HT_4) receptor agonist. This agonistic action may result in increased gastrointestinal motility and cardiac rate.

ESOPHAGUS: Single doses of cisapride (4 mg to 10 mg IV) increased the lower esophageal sphincter pressure (LESP) and lower esophageal peristalsis compared to placebo and/or metoclopramide. In patients with gastroesophageal reflux disease (GERD) and a LESP of <10 mm Hg, cisapride dose-dependently increased the strength of esophageal peristalsis and more than doubled LESP, raising it to normal values. The increase in LESP was partially reversed by atropine, suggesting that the effect is partly, but not exclusively, cholinergically-mediated. Twenty mg oral cisapride given once to healthy volunteers similarly increased LESP, starting 45 minutes after dosing, with a peak response at 75 minutes. The full duration of the effect was not monitored, and doses smaller than 20 mg were ineffective. Ten mg oral cisapride, administered 3 times daily for several days to patients with GERD, resulted in a significant increase in LESP, and an increased esophageal acid clearance.

STOMACH: Cisapride (single 10 mg doses IV or oral or 10 mg given orally 3 times daily up to six weeks) significantly accelerated gastric emptying of both liquids and solids. Acceleration of gastric emptying, measured over a four hour period following a radio-labeled test meal given at lunch time, was greatest when 10 mg cisapride was given both in the morning and again before the test meal, intermediate when 20 mg was given as a single administration in the morning and least when only 10 mg was given on the morning of the test meal. The increases in gastric emptying were proportional to the plasma levels of cisapride measured in these subjects over the same 4 hours that the gastric emptying test was conducted.

Clinical Trials

Clinical trials have shown that cisapride can reduce the symptoms of nocturnal heartburn associated with gastroesophageal reflux disease. Two placebo-controlled studies, one using a dose of 10 mg QID, the other both 10 mg and 20 mg QID, showed effects on nighttime heartburn, although the 10 mg dose in the second study was only marginally effective. There were no consistent effects on daytime heartburn, symptoms of regurgitation, or histopathology of the esophagus. Use of antacids was only infrequently affected and slightly decreased. In a third

controlled trial of similar design to the others, neither 10 mg nor 20 mg taken 4 times was superior to placebo.

These clinical trials did not show a significant effect on LESP, perhaps because the majority of these patients had normal LESP's at the beginning and end of the study period. In a clinical trial comparing 10 mg cisapride to placebo, pH probe evaluation, in a relatively small number of patients, did not reveal a significant difference in pH.

INDICATIONS AND USAGE

Cisapride oral suspension is indicated for the symptomatic treatment of patients with nocturnal heartburn due to gastroesophageal reflux disease.

CONTRAINDICATIONS

Concomitant administration of ketoconazole, itraconazole, miconazole, fluconazole, erythromycin, clarithromycin, or troleandomycin with cisapride is contraindicated (See WARNINGS and PRECAUTIONS - Drug Interactions).

Cisapride should not be used in patients in whom an increase in gastrointestinal motility could be harmful, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation.

Cisapride is contraindicated in patients with known sensitivity or intolerance to the drug.

WARNINGS

Cisapride undergoes metabolism mainly by the hepatic cytochrome P450 3A4 isoenzyme. Drugs which inhibit this enzyme such as ketoconazole, itraconazole, miconazole, clarithromycin, erythromycin, fluconazole, or troleandomycin can lead to elevated cisapride blood levels.

Rare cases of serious cardiac arrhythmias, including ventricular arrhythmias and torsades de pointes associated with QT prolongation, have been reported in patients taking cisapride with ketoconazole, itraconazole, miconazole, erythromycin, clarithromycin, or fluconazole. Some of these patients did not have known cardiac histories; however, most had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. Some of these cases have been fatal.

PRECAUTIONS

General
Potential benefits should be weighed against risks prior to administration of cisapride to patients with conditions associated with QT prolongation, such as congenital prolonged QT syndrome, uncorrected electrolyte disturbances or in patients who are taking other medications known to prolong QT interval.

Information for Patients
Patients should be warned against concomitant use of oral ketoconazole, itraconazole, miconazole, erythromycin, clarithromycin, fluconazole, or troleandomycin with cisapride.

Although cisapride does not affect psychomotor function nor does it induce sedation or drowsiness when used alone, patients should be advised that the sedative effects of benzodiazepines and of alcohol may be accelerated by cisapride.

Drug Interactions
Cisapride is metabolized mainly via the cytochrome P450 3A4 enzyme.

Human pharmacokinetic data indicate that oral ketoconazole potently inhibits the metabolism of cisapride, resulting in a mean eight-fold increase in AUC of cisapride. A study in 14 normal male and female volunteers suggests that coadministration of cisapride and ketoconazole can result in prolongation of the QT interval on the ECG.

In vitro data indicate that itraconazole, miconazole, fluconazole, erythromycin, clarithromycin, and troleandomycin also markedly inhibit cytochrome P450 3A4 mainly responsible for the metabolism of cisapride.

In some cases where serious ventricular arrhythmias, QT prolongation, and torsades de pointes have occurred when cisapride was taken in conjunction with one of the cytochrome P450 3A4 inhibitors, elevated blood cisapride levels were noted at the time of the QT prolongation. Normalization of the QT interval after cisapride was discontinued has been observed.

Concurrent administration of anticholinergic compounds would be expected to compromise the beneficial effects of cisapride.

The acceleration of gastric emptying by cisapride could affect the rate of absorption of other drugs. Patients receiving narrow therapeutic ratio drugs or other drugs that require careful titration should be followed closely; if plasma levels are being monitored, they should be reassessed.

In patients receiving oral anticoagulants, the coagulation times were increased in some cases. It is advisable to check coagulation time within the first few days after the start and discontinuation of cisapride therapy, with an appropriate adjustment of the anticoagulant dose, if necessary.

Cimetidine coadministration leads to an increased peak plasma concentration and AUC of cisapride; there is no effect on cisapride absorption when it is coadministered with ranitidine. The gastrointestinal absorption of cimetidine and ranitidine is accelerated when they are coadministered with cisapride.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a twenty-five month oral carcinogenicity study in rats, cisapride at daily doses up to 80 mg/kg was not tumorigenic. For a 50 kg person of average height (1.46 m^2 body surface area), this dose represents 50 times the maximum recommended human dose (1.6 mg/kg/day) on a mg/kg basis and 7 times the maximum recommended human dose (54.4 mg/m^2) on a body surface area basis. In a nineteen month oral carcinogenicity study in mice, cisapride at daily doses up to 80 mg/kg was not tumorigenic. This dose represents 50 times the maximum recommended human dose on a mg/kg basis and about 4 times the maximum recommended human dose on a body surface area basis.

Cisapride was not mutagenic in the *in vitro* Ames test, human lymphocyte chromosomal aberration test, mouse lymphoma cell forward mutation test, and rat hepatocyte UDS test and *in vivo* rat micronucleus test, male and female mouse dominant lethal mutations tests, and sex linked recessive lethal test in male *Drosophila melanogaster*.

Fertility and reproductive performance studies were conducted in male and female rats. Cisapride was found to have no effect on fertility and reproductive performance of male rats at oral doses up to 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m^2 basis). In the female rats, cisapride at oral doses of 40 mg/kg/day and higher prolonged the breeding interval required for impregnation. Similar effects were also observed at maturity in the female offspring (F_1) of the female rats (F_0) treated with oral doses of cisapride at 10 mg/kg/day or higher. Cisapride at an oral dose of 160 mg/kg/day also exerted contragestational/pregnancy disrupting effects in female rats (F_0).

Pregnancy

TERATOGENIC EFFECTS, PREGNANCY CATEGORY C

Oral teratology studies have been conducted in rats (doses up to 160 mg/kg/day) and rabbits (doses up to 40 mg/kg/day). There was no evidence of a teratogenic potential of cisapride in rats or rabbits. Cisapride was embryotoxic and fetotoxic in rats at a dose of 160 mg/kg/day (100 times the maximum recommended human dose on a mg/kg basis and 14 times the maximum recommended human dose on a mg/m^2 basis) and in rabbits at a dose of 20 mg/kg/day (approximately 12 times the maximum recommended human dose on a mg/kg basis) or higher. It

also produced reduced birth weights of pups in rats at 40 and 160 mg/kg/day and adversely affected the pup survival. There are no adequate and well-controlled studies in pregnant women. Cisapride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Cisapride is excreted in human milk at concentrations approximately one twentieth of those observed in plasma. Caution should be exercised when cisapride is administered to a nursing woman, and particular care must be taken if the nursing infant or the mother is taking a drug that might alter cisapride's metabolism in the infant. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS - Drug Interactions).

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Steady-state plasma levels are generally higher in older than in younger patients, due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

The rate of adverse experiences in patients greater than 65 years of age was similar to that in younger adults.

ADVERSE REACTIONS

In the U.S. clinical trial population of 1728 patients (comprising 506 with gastroesophageal reflux disorders, and the remainder with other motility disorders) the following adverse experiences were reported in more than 1% of patients treated with cisapride and at least as often on cisapride as on placebo. The percent of patients who discontinued treatment is displayed in parentheses.

SYSTEM/ADVERSE EVENT	**CISAPRIDE N=1042**	**PLACEBO N=686**
Central & Peripheral Nervous Systems		
Headache	19.3% (1.1%)	17.1% (0.4%)
Gastrointestinal		
Diarrhea	14.2 (0.7)	10.3 (0.1)
Abdominal pain	10.2 (1.2)	7.7 (0.9)
Nausea	7.6 (1.0)	7.6 (0.3)
Constipation	6.7 (0.1)	3.4 (0.0)

Flatulence	3.5 (0.4)	3.1 (0.4)
Dyspepsia	2.7 (0.1)	1.0 (0.0)
Respiratory System		
Rhinitis	7.3 (0.1)	5.7 (0.1)
Sinusitis	3.6 (0.0)	3.5 (0.0)
Coughing	1.5 (0.2)	1.2 (0.0)
Resistance Mechanism		
Viral infection	3.6 (0.2)	3.2 (0.0)
Upper respiratory tract infection	3.1 (0.0)	2.8 (0.0)
Body as a Whole		
Pain	3.4 (0.0)	2.3 (0.0)
Fever	2.2 (0.1)	1.5 (0.0)
Urinary System		
Urinary tract infection	2.4 (0.0)	1.9 (0.0)
Micturition frequency	1.2 (0.1)	0.6 (0.0)
Psychiatric		
Insomnia	1.9 (0.3)	1.3 (0.4)
Anxiety	1.4 (0.1)	1.0 (0.1)
Nervousness	1.4 (0.2)	0.7 (0.0)
Skin & Appendages		
Rash	1.6 (0.0)	1.6 (0.3)
Pruritus	1.2 (0.1)	1.0 (0.0)
Musculoskeletal System		
Arthralgia	1.4 (0.1)	1.2 (0.0)
Vision		
Abnormal vision	1.4 (0.2)	0.3 (0.0)
Reproductive, Female		
Vaginitis	1.2 (0.0)	0.9 (0.0)

The following adverse events also reported in more than 1% of cisapride patients were more frequently reported on placebo: dizziness, vomiting, pharyngitis, chest pain, fatigue, back pain, depression, dehydration, and myalgia.

Diarrhea, abdominal pain, constipation, flatulence, and rhinitis all occurred more frequently in patients using 20 mg of cisapride than in patients using 10 mg.

Additional adverse experiences reported to occur in 1% or less of patients in the U.S. clinical studies are: dry mouth, somnolence, palpitation, migraine, tremor, and edema.

In other U.S. and international trials and in foreign marketing experience, there have been rare reports of seizures and extrapyramidal effects, tachycardia, elevated liver enzymes, hepatitis, thrombocytopenia, leukopenia, aplastic anemia, pancytopenia, and granulocytopenia. The relationship of cisapride to the event was not clear in these cases.

There have been rare cases of sinus tachycardia reported. Rechallenge precipitated relapse in some of those patients.

Rare cases of cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, torsades de pointes and QT prolongation, in some cases resulting in death, have been reported. Most of these patients had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. A causal relationship to cisapride has not been established.

OVERDOSAGE

Reports of overdosage with cisapride include an adult who took 540 mg and for 2 hours experienced retching, borborygmi, flatulence, stool frequency and urinary frequency.

A one-month old male infant received 2 mg/kg of cisapride, 10 times the prescribed dose, four times per day for 5 days. The patient developed third degree heart block and subsequently died of right ventricular perforation caused by pacemaker wire insertion.

Treatment should include gastric lavage and/or activated charcoal, close observation and general supportive measures.

In instances of overdose, patients should be evaluated for possible QT prolongation and for factors that can predispose to the occurrence of ventricular arrhythmias, including torsades de pointes.

Single oral doses of cisapride at 4000 mg/kg, 160 mg/kg, 1280 mg/kg and 640 mg/kg were lethal in adult rats, neonatal rats, mice and dogs, respectively. Symptoms of acute toxicity were ptosis, tremors, convulsions, dyspnea, loss of righting reflex, catalepsy, catatonia, hypotonia and diarrhea.

DOSAGE AND ADMINISTRATION

5 mL (1 teaspoonful) suspension = 5 mg

Adults
Initiate therapy with 10 mL of cisapride oral suspension 4 times daily at least 15 minutes before meals and at bedtime. In some patients the dosage will need to be increased to 20 mg, given as above, to obtain a satisfactory result.

In elderly patients, steady-state plasma levels are generally higher due to a moderate prolongation of the elimination half-life. Therapeutic doses, however, are similar to those used in younger adults.

HOW SUPPLIED

Cisapride Oral Suspension contains the equivalent of 1 mg/mL of cisapride.

- Packaging, NDC number
- Color and flavor of suspension
  Note: The innovator's oral suspension is a bright pink homogenous suspension containing 1 mg/mL of cisapride and is supplied in 16 fl oz bottles.
- Store at room temperature 15° - 25°C (59° - 77°F).
- "Caution: Federal Law..." statement.

Include the following information at the end of the HOW SUPPLIED section:

- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.

CONTAINER LABEL

In addition to the general label requirements ("Caution: Federal Law..." statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name and strength should read as follows:

CISAPRIDE ORAL SUSPENSION

5 mg/mL*

Side Panel:

- Each 5 mL contains statement should read as follows:

*Each 5 mL contains cisapride as the monohydrate equivalent to 5 mg of cisapride.

- Include “Usual Dosage” statement.
- Store at room temperature 15° - 25°C (59° - 77°F).
- Include a “Dispense in...” statement.